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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,836	03/15/2006	Jialin Sun	09548.1019USWO	3476

52835 7590 08/27/2007

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EXAMINER	
GUSSOW, ANNE	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
08/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/571,836	SUN, JIALIN	
	Examiner	Art Unit	
	Anne M. Gussow	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,11-16 and 21-30* is/are pending in the application.

4a) Of the above claim(s) *27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,11-16 and 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *March 15, 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/15/06, 7/6/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1, 2, and 11-16, in the reply filed on July 6, 2007 is acknowledged. The traversal is on the ground(s) that the claims possess unity of invention because the Pseudomonas exotoxin (PE) taught by Kihara and Pastan (as cited in the previous office action) is not a superantigen. This argument has been carefully considered and although the PE is not a superantigen, Wahlsten, et al. (Journal of Immunology, 1998. Vol. 161, pages 6761-6767) teach a fusion protein comprising the superantigen TSST1 fused to the transmembrane region of the proto-oncogene c-*erb*-B-2 (abstract). Thus, the technical feature of claim 1, a fusion protein comprising a ligand that stimulates cancer cell growth and a superantigen, is not special.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 27-30 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 6, 2007.

3. Claims 21-30 have been added.

Claims 1, 2, 11-16, and 21-26 are under examination.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on March 15, 2006 and July 6, 2007 have been considered by the examiner and an initialed copy of the IDS is included with the mailing of this Office Action.

Specification

5. The disclosure is objected to because of the following informalities: the specification contains typographical errors, for example, on page 1 "superatnigens" should read "superantigens".

Appropriate correction is required throughout.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2, 11, and 21-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for fusion proteins comprising a ligand that stimulates cancer cell growth and a superantigen, does not reasonably provide enablement for natural variants or variants with 70% or more identity to the ligands. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or used the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a fusion protein comprising a ligand that stimulates cancer cell growth and corresponds to receptors overexpressed by cancer cells, or a screened peptide that is affinitive to or antagonist to cancer cell receptors, or a peptide that directly interacts with cancer cell surface, and a superantigen that may lead to anti-cancer immune response, wherein the ligand that stimulates cancer cell growth and corresponds to receptors overexpressed by cancer cells is selected from: epidermal growth factor (EGF) family, vascular endothelial cell growth factor (VEGF) family, basic fibroblast growth factor bFGF and FGF family, transforming growth factor-a (TGF-a), interleukin-4, interleukin-2, interleukin-6, interleukin-13, interleukin-3, granulocyte-macrophage colony-stimulating factor (GM-CSF), heparin-binding EGF-like growth factor (HB-EGF), insulin-like growth factor (IGF), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), nerve growth factor (NGF), placental growth factor (PGF), stem cell factor (SCF), interleukin-8, Ephrin family, Heregulin, erbB ligand, chemokine, angiopoietin (Ang), thrombopoietin (TPO), factor VII, urokinase-type plasminogen activator (uPA), growth hormone releasing hormone, gonadotropin-

releasing hormone (GRH), a-melanocyte stimulating hormone (a-MSH), gastrin-releasing peptide (GRP), prolactin (PRL), prolactin releasing hormone (PRLH), growth hormone, follicle stimulating hormone (FSH), placental lactogen (PL), chorionic gonadotropin (CG), corticotrophin releasing hormone, somatostatin, asialoglycoprotein, low density lipoprotein and transferring, and other ligands associated with cancers or immune diseases, and their nature variants and artificial variants with more than 70% identity, and artificial polypeptides that interact with cancer cell surface receptors, wherein the amino acid sequence of natural variants and artificial variants is at least 70% identical to that of the ligands.

The claims are also broadly drawn to a fusion protein, wherein the fusion protein comprises: a) a ligand from epidermal growth factor (EGF) family and their nature variants and artificial variants with more than 70% identity; b) a superantigen that may lead to anti-cancer immune response, wherein the amino acid sequence of natural variants and artificial variants is at least 70% identical to that of the ligands, wherein the superantigen that leads to anti-cancer immune response is selected from: Staphylococcal enterotoxin (SE), Streptococcus pyogenes exotoxin (SPE), Staphylococcus aureus toxic shock-syndrome toxin (TSST), Streptococcal mitogenic extotoxin (SME), Streptococcal superantigen (SSA), vital protein and the nature and artificial variants thereof, wherein the Staphylococcal enterotoxin is selected from SEA, SEB, SEC, SED, SEE, SEG SHE, SEI, SEJ, SEK, SEL, SEM, SER and SET, wherein the ligand that stimulates cancer cell growth and corresponds to receptors overexpressed by cancer cells is selected from epidermal growth factor (EGF) and

vascular endothelial cell growth factor (VEGF), wherein the superantigen that leads to anti-cancer immune response is SEA of Staphylococcal enterotoxin family.

The specification discloses fusion proteins consisting of EGF fused to an SEA superantigen and VEGF fused to an SEA superantigen. The specification does not disclose proteins having 70% identity to the EGF or VEGF ligands.. The specification does not disclose natural or artificial variants of the ligands.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology, 1990. Vol. 111, pages 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar, et al. Molecular and Cellular Biology, 1988. Vol. 8 No. 3, pages 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin (Schwartz, et al. Proc Natl Acad Sci, 1987. Vol. 84, pages 6408-6411). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase (Lin, et al. Biochemistry, 1975. Vol. 14, pages 1559-1563).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect

the biological activity of the protein. Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. The results of the construction of synthetic proteins remain very unpredictable as Burgess et al, Lazar et al, Schwartz et al, and Lin et al conclusively demonstrate.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 2, 11, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Wahlsten, et al. (Journal of Immunology, 1998. Vol. 161, pages 6761-6767).

The claims recite a fusion protein, wherein the fusion protein comprises: a) a ligand that stimulates cancer cell growth and corresponds to receptors overexpressed by cancer ceils, or a screened peptide that is affinitive to or antagonist to cancer cell receptors, or a peptide that directly interacts with cancer cell surface; b) a superantigen that may lead to anti-cancer immune response, wherein the ligand that

stimulates cancer cell growth and corresponds to receptors overexpressed by cancer cells is selected from: epidermal growth factor (EGF) family, vascular endothelial cell growth factor (VEGF) family, basic fibroblast growth factor bFGF and FGF family, transforming growth factor-a (TGF-a), interleukin-4, interleukin-2, interleukin-6, interleukin-13, interleukin-3, granulocyte-macrophage colony-stimulating factor (GM-CSF), heparin- binding EGF-like growth factor (HB-EGF), insulin-like growth factor (IGF), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), nerve growth factor (NGF), placental growth factor (PGF), stem cell factor (SCF), interleukin-8, Ephrin family, Heregulin, erbB ligand, chemokine, angiopoietin (Ang), thrombopoietin (TPO), factor VII, urokinase-type plasminogen activator (uPA), growth hormone releasing hormone, gonadotropin-releasing hormone (GRH), a-melanocyte stimulating hormone (a,-MSH), gastrin-releasing peptide (GRP), prolactin (PRL), prolactin releasing hormone (PRLH), growth hormone, follicle stimulating hormone (FSH), placental lactogen (PL), chorionic gonadotropin (CG), corticotrophin releasing hormone, somatostatin, asialoglycoprotein, low density lipoprotein and transferring, and other ligands associated with cancers or immune diseases, and their nature variants and artificial variants with more than 70% identity, and artificial polypeptides that interact with cancer cell surface receptors, wherein the amino acid sequence of natural variants and artificial variants is at least 70% identical to that of the ligands, wherein the superantigen that leads to anti-cancer immune response is selected from: Staphylococcal enterotoxin (SE), Streptococcus pyogenes cxotoxin (SPE), Staphylococcus aureus toxic shock-syndrome toxin (TSST), Streptococcal mitogenic

extotoxin (SME), Streptococcal superantigen (SSA), viral protein and the nature and artificial variants thereof.

Wahlsten, et al. teach fusion proteins for inducing an immune response to tumor cells wherein a superantigen, TSST1 is fused to the transmembrane (TM) region of the proto oncogene c-*erb*-B-2. Since the claims require that the ligand peptide interact with the cell surface, and Wahlsten, et al's construct binds to the surface of MA148 cells (a human ovarian carcinoma cell line), all the limitations of the claims have been met.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 1, 2, 11-16, and 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wahlsten, et al. (Journal of Immunology, 1998. Vol. 161, pages

6761-6767) in view of Chandler, et al. (International Journal of Cancer, 1998. Vol. 78, pages 106-111).

Claims 1, 2, 11, and 12 have been described supra. Claims 13-16, and 21-16 recite a fusion protein according to claim 12, wherein the Staphylococcal enterotoxin is selected from SEA, SEB, SEC, SED, SEE, SEG, SHE, SEI, SEJ, SEK, SEL, SEM, SER and SET, wherein the Streptococcus pyogenes exotoxin is selected from SPE-A, SPE-B, SPE-C, SPE-F, SPE-G, SPE-H, SPE-I, SPE, J, SPE-L and SPE-M. A fusion protein according to claim 1, wherein the ligand that stimulates cancer cell growth and corresponds to receptors overexpressed by cancer cells is selected from epidermal growth factor (EGF) and vascular endothelial cell growth factor (VEGF), wherein the superantigen that leads to anti-cancer immune response is SEA of Staphylococcal enterotoxin family, wherein the superantigen is SEA protein, and the ligand is selected from epidermal growth factor (EGF) and vascular endothelial cell growth factor (VEGF). The claims also recite a fusion protein, wherein the fusion protein comprises: a) a ligand from epidermal growth factor (EGF) family and their natural variants and artificial variants with more than 70% identity; b) a superantigen that may lead to anti-cancer immune response, wherein the amino acid sequence of natural variants and artificial variants is at least 70% identical to that of the ligands, wherein the superantigen that leads to anti-cancer immune response is selected from: Staphylococcal enterotoxin (SE), Strcptocoocus pyogenes exotoxin (SPE), Staphylococcus aureus toxic shock-syndrome toxin (TSST), Streptococcal mitogenic extotoxin (SME), Streptococcal superantigen (SSA), vital protein and the natural and artificial variants thereof, wherein

the Staphylococcal enterotoxin is selected from SEA, SEB, SEC, SED, SEE, SEG SHE, SEI, SEJ, SEK, SEL, SEM, SER and SET, wherein the ligand that stimulates cancer cell growth and corresponds to receptors overexpressed by cancer cells is selected from epidermal growth factor (EGF) and vascular endothelial cell growth factor (VEGF), wherein the superantigen that leads to anti-cancer immune response is SEA of Staphylococcal enterotoxin family.

Wahlsten, et al. has been described supra. Wahlsten, et al. teach a fusion protein consisting of the superantigen TSST1 and the transmembrane sequence of the proto-oncogene c-erb-B-2. Wahlsten, et al. do not teach a member of the epidermal growth factor family fused to the superantigen SEA. These deficiencies are made up for in the teachings of Chandler, et al.

Chandler, et al. teach a fusion protein comprising heparin-binding epidermal growth factor (HB-EGF) and the plant ribosome-inactivating protein saporin (SAP).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a fusion protein comprising the EGF family member ligand of Chandler, et al. and the superantigen as taught by Wahlsten, et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a fusion protein comprising the EGF family member ligand of Chandler, et al. and the superantigen of Wahlsten, et al. because Chandler, et al. teach an HB-EGF fused to an antigen for binding to tumor cells. Additionally, since Wahlsten et al. teach a cell ligand (TM) fused to a

superantigen, one of skill in the art would be able to exchange the TSST1 superantigen for any other known superantigen with reasonable expectation of success. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the HB-EGF ligand of Chandler and produce a fusion protein with an SEA superantigen in view of Wahlsten, et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made, as evidenced by the references.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571) 272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

August 16, 2007

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER